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A Decade of Induction Chemotherapy Practices at a Small Children's Cancer Center

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Introduction

Across the United States, children diagnosed with acute lymphoblastic leukemia (ALL) following Children's Oncology Group (COG) protocols undergo standard 3 or 4-drug induction chemotherapy. However, length of stay (LOS) and antibiotic practices during induction chemotherapy vary by institution. Much less is known about hospital practices and outcomes during induction chemotherapy from small institutions similar to ours. At our institution, there are on average 30 to 35 newly diagnosed oncology patients every year. Previously, our hospital practice included keeping high risk patients undergoing 4-drug induction chemotherapy longer in the hospital through absolute neutrophil count (ANC) nadir prior to discharge home. According to Wedekind et al,[1] long LOS hospitals had lower odds of any readmission. Of note, such odds were higher in patients >10 years or girls, with the top 2 most common diagnoses at readmission being neutropenia and fever.[1] Literature suggests that infectious complications occur in 20-35% of patients undergoing induction chemotherapy. Slone et al[2] found 39% of patients had infectious complications during induction chemotherapy with a 25% readmission rate. According to Sulis et al,[3] reported bacterial infections during induction chemotherapy accounted for 25% of patients. Other factors such as young age, white race, intensive chemotherapy, and lack of neutrophil surge after dexamethasone treatment was associated with infection-related complications.[4] After several infectious complications in one year at our institution, the purpose of this retrospective review was to evaluate the influence of our hospital practices in relation to morbidity during induction chemotherapy within the last decade of care.

Methods

- Retrospective chart review
- Inclusion criteria: Patients 1 to 21 years of age with newly diagnosed ALL or lymphoblastic lymphoma (LLy) at our institution between May 1, 2020 and May 31, 2020
- Exclusion criteria: infant ALL, acute myeloid leukemia (AML), and Down's Syndrome
- Eligible patients had to complete entirety of induction chemotherapy at our institution
- Infectious complications during initial hospitalization were defined as documented bacterial infection during hospital stay prior to discharge. This included positive microbiological culture, sepsis, clinical findings of abscess or cellulitis, and/or radiological evidence of deep soft tissue infection.
- Readmission infectious complication was defined as documented bacterial infection or fever on readmission.
- Length of stay (LOS) categorized as the following, taking into account for patients with weekend admissions and time to chemotherapy initiation:
  - Short LOS ≤11 days
  - Medium LOS 12-15 days
  - Long LOS ≥16 d
- Fever was defined as at least one oral temperature of 38.3°C or two consecutive temperatures of 38°C in 1 hour.
- Readmission period included the first 30 days following the initial day of admission for diagnosis and induction chemotherapy.

Statistical Analysis

The primary outcome was to evaluate infectious complications and readmission rates during induction chemotherapy. Two patient groups were compared in regard to LOS, type of induction, age, sex, comorbidities, risk stratification, and central line type utilizing t-test, where appropriate. Two-sided tests of significance were utilized and a $P< 0.05$ were specified as statistically significant. A multivariate analysis has not been performed yet.

Results

Of the 72 patients, 14 (19%) had infectious complications during the entirety of induction chemotherapy (Table II). Only 9 (13%) patients were readmitted for infectious complications or fever. The most common infectious complication during induction chemotherapy included bacteremia and neutropenic fever (Table II). The most common organism found on readmission was methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia (56%). Patients undergoing 3-drug induction had increased rates of infectious complications during induction chemotherapy as compared to those undergoing 4-drug induction (Table III).

Table I: Demographic characteristics of the 72 patients during induction chemotherapy

	N (%)	*P*-value
Age		
1-10 years	53 (74%)	
>10 years	19 (26%)	**<0.00001**
Sex		
Female	30 (42%)	
Male	42 (58%)	0.0549
Race		
White	52 (72%)	
African American	4 (6%)	
Asian	1 (1%)	
Other	10 (14%)	
Unknown	5 (7%)	
Ethnicity		
Hispanic	13 (18%)	
Non-Hispanic	57 (79%)	
Unknown	2 (3%)	
Comorbidities		
Yes	68 (94%)	
No	4 (6%)	**<0.00001**
Central line type		
PICC	44 (61%)	
MediPort	28 (39%)	**0.0083**
ALL categorization		
B-ALL	60 (83%)	
T-ALL	9 (13%)	
T-LLy	3 (4%)	
ALL risk stratification		
High risk B-ALL	22 (31%)	
Standard risk B-ALL	38 (53%)	**0.0076**
Chemotherapy protocol		
3-drug induction	40 (56%)	
4-drug induction	32 (44%)	0.1499

PICC, peripherally inserted central catheter; B-ALL, B-cell acute lymphoblastic leukemia; T-ALL, T-cell acute lymphoblastic leukemia; T-LLy, T-cell lymphoblastic lymphoma.

Table II: Infectious complication characteristics during induction chemotherapy

	N (%)
Total Infectious Complications	**14 (19%)**
Bacteremia	
Methicillin-susceptible Staphylococcus aureus[a]	5 (36%)
Escherichia coli[b]	1 (7%)
Pseudomonas	1 (7%)
Group B streptococcus	1 (7%)
Streptococcus pneumoniae	1 (7%)
Moraxella	1 (7%)
Sepsis, blood culture negative	1 (7%)
C. *difficile* infection	1 (7%)
Neutropenic fever	5 (36%)
Non-neutropenic fever	1 (7%)
Osteomyelitis	1 (7%)
Pyomyositis	1 (7%)
Intussusception	1 (7%)
Ecthyma	1 (7%)

[a]On readmission, Methicillin-susceptible Staphylococcus aureus bacteremia was the predominate organism found at 56%

[b]Escherichia coli bacteremia was the second most common organism at 11%; MRSA, Methicillin-resistant Staphylococcus aureus was not found. No deaths were identified.

Table III: Infectious complications during induction chemotherapy between those undergoing 3-drug verse 4-drug induction chemotherapy protocols

Chemotherapy protocol	N (%)
3-drug induction	9 (64%)
4-drug induction	5 (36%)

There were significant differences in LOS. Twenty-two of the 40 patients (55%) who received 3-drug induction had short LOS (≤11 d) as compared to 5 (16%) of the 32 patients with 4-drug induction (P=0.0007). Contrary, 26 (81%) of these patients had long LOS (≥16 d) as compared to 10 (25%) of patients who received 3-drug induction (P=<0.00001). Both of these findings were statistically significant (Table IV). Most of the few patients undergoing 4-drug induction chemotherapy with short LOS were readmitted with infectious complications (60%). This was also statistically significant. Interestingly, most of the readmitted patients were <10 years of age (Table V).

Table IV: Length of stay and readmission rate for infectious complications between those patients undergoing 3-drug verse 4-drug induction chemotherapy protocols

	Short LOS[a] (%) (range)	Medium LOS[b] (%) (range)	Long LOS[c] (%) (range)
Induction protocol			
3-drug induction (N=40)	22 (55%) (6-11d)	8 (20%) (12-14d)	10 (25%) (15-30d)
4-drug induction (N=32)	5 (16%) (6-10d)	1 (13%) (13d)	26 (81%) (16-33d)
P-value	**0.0007**	0.429	**<0.00001**
Readmission rate			
3-drug induction (N=40)	1 (5%)	2 (25%)	2 (20%)
4-drug induction (N=32)	3 (60%)	0	1 (4%)
P-value	**0.002**	0.569	0.121

LOS, length of stay; [a]Short LOS defined as ≤11 days; [b]Medium LOS defined as 12-15 days; [c]Long LOS defined as ≥16 days.

Table V: Readmission rate for infectious complications evaluated by age

	N (%)	*P*-value
Readmission rate		
Age <10 years	7 (78%)	**0.017**
Age ≥10 years	2 (22%)	

Conclusion

We found lower (19%) but comparable total rate of infectious complications during ALL induction chemotherapy as reported in the literature.[2,3] However, our rate of readmission (13%) as well as rates of infectious complications or fever when readmitted, was much lower. Furthermore, when stratified by NCI risk group or 3-drug vs. 4-drug induction, we did not see a difference. Similarly, to Inaba et al,[4] we found that young age (<10 years) was associated with increased rate of infectious complications on readmission during induction (78%). Limits of the study include the retrospective nature of the review as well as the lack of a robust statistical analysis that accounted for a variety of factors including multivariate analysis. Our study demonstrated that patients undergoing 4-drug induction chemotherapy who had a short LOS (≤11 days) had increased rates of readmission and infectious complications. On the contrary, patients undergoing 3-drug induction chemotherapy with short LOS had lower rates of readmission for infectious complications. We believe the practice of keeping SR patients until at least day 8 of induction and most of those receiving 4-drug induction past absolute neutrophil count nadir or LOS ≥16 days, may account for our favorable findings. Now, with literature supporting levofloxacin prophylaxis during induction chemotherapy for prevention of febrile neutropenia and systemic infection5, earlier discharge for high-risk patients is a consideration.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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